Clinical Ascertainment of Health Outcomes Among Adults Treated for Childhood Cancer

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Importance Adult survivors of childhood cancer are known to be at risk for treatment-related adverse health outcomes. A large population of survivors has not been evaluated using a comprehensive systematic clinical assessment to determine the prevalence of chronic health conditions.

Objective To determine the prevalence of adverse health outcomes and the proportion associated with treatment-related exposures in a large cohort of adult survivors of childhood cancer.

Design, Setting, and Participants Presence of health outcomes was ascertained using systematic exposure–based medical assessments among 1713 adult (median age, 32 [range, 18-60] years) survivors of childhood cancer (median time from diagnosis, 25 [range, 10-47] years) enrolled in the St Jude Lifetime Cohort Study since October 1, 2007, and undergoing follow-up through October 31, 2012.

Main Outcomes and Measures Age-specific cumulative prevalence of adverse outcomes by organ system.

Results Using clinical criteria, the crude prevalence of adverse health outcomes was highest for pulmonary (abnormal pulmonary function, 65.2% [95% CI, 60.4%-69.8%]), auditory (hearing loss, 62.1% [95% CI, 55.8%-68.2%]), endocrine or reproductive (any endocrine condition, such as hypothalamic-pituitary axis disorders and male germ cell dysfunction, 62.0% [95% CI, 59.5%-64.6%]), cardiac (any cardiac condition, such as heart valve disorders, 56.4% [95% CI, 53.5%-59.2%]), and neurocognitive (neurocognitive impairment, 48.0% [95% CI, 44.9%-51.0%]) function, whereas abnormalities involving hepatic (liver dysfunction, 13.0% [95% CI, 10.8%-15.3%]), skeletal (osteoporosis, 9.6% [95% CI, 8.0%-11.5%]), renal (kidney dysfunction, 5.0% [95% CI, 4.0%-6.3%]), and hematopoietic (abnormal blood cell counts, 3.0% [95% CI, 2.1%-3.9%]) function were less common. Among survivors at risk for adverse outcomes following specific cancer treatment modalities, the estimated cumulative prevalence at age 50 years was 21.6% (95% CI, 19.3%-23.9%) for cardiomyopathy, 83.5% (95% CI, 80.2%-86.8%) for heart valve disorder, 81.3% (95% CI, 77.6%-85.0%) for pulmonary dysfunction, 76.8% (95% CI, 73.6%-80.0%) for pituitary dysfunction, 86.5% (95% CI, 82.3%-90.7%) for hearing loss, 31.9% (95% CI, 28.0%-35.8%) for primary ovarian failure, 31.1% (95% CI, 27.3%-34.9%) for Leydig cell failure, and 40.9% (95% CI, 32.0%-49.8%) for breast cancer. At age 45 years, the estimated cumulative prevalence of any chronic health condition was 95.5% (95% CI, 94.8%-98.6%) and 80.5% (95% CI, 73.0%-86.6%) for a serious/disabling or life-threatening chronic condition.

Conclusions and Relevance Among adult survivors of childhood cancer, the prevalence of adverse health outcomes was high, and a systematic risk-based medical assessment identified a substantial number of previously undiagnosed problems that are more prevalent in an older population. These findings underscore the importance of ongoing health monitoring for adults who survive childhood cancer.

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CURATIVE THERAPY FOR PEDIATRIC malignancies has produced a growing population of adults formerly treated for childhood cancer who are at risk for health problems[1-3] that appear to increase with aging.[2-5] The prevalence of cancer-related toxic effects that are systematically ascertained through formal clinical assessments has not been well studied. Ongoing clinical evaluation of well-characterized cohorts is important to advance knowledge about the influence of aging on cancer-related morbidity and mortality and to guide the development of health screening recommendations and health-preserving interventions.

The objective of this investigation was to determine, through systematic comprehensive medical assessment, the general health status of long-term survivors of childhood cancer and the prevalence of treatment complica-

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tions following predisposing cancer treatment–related exposures.

METHODS

Participants

Following provision of written informed consent, eligible survivors were enrolled in the ongoing institutional review board–approved St Jude Lifetime Cohort Study (SJLIFE) using recruitment strategies described previously.[6,7] The objective of SJLIFE is to establish a lifetime cohort of survivors treated at St Jude Children's Research Hospital to facilitate prospective periodic medical assessment of health outcomes among adults surviving pediatric malignancies. Eligibility for SJLIFE includes age 18 years or older, treatment for cancer at St Jude, and survival 10 or more years after diagnosis. The order of recruitment of eligible survivors was randomly determined by allocating participants to blocks of 50. This study included participants who were within the first 59 consecutive recruitment blocks (eFigure 1 available at http://www.jama.com).

Medical record abstraction documented the type and cumulative doses of treatment, information on surgical interventions, acute life-threatening organ toxic effects, primary cancer recurrences, chronic health conditions, and subsequent neoplasms. Race and ethnicity were self-reported by participants and ascertained for nonparticipants by administrative record review of race/ethnicity reported by parents at diagnosis. Participants completed comprehensive health questionnaires prior to their clinical assessment.

All participants underwent a core battery of evaluations comprising a history and physical examination with measurement of resting heart rate and blood pressure, 12-lead electrocardiography, and laboratory studies including complete blood cell count with differential, comprehensive metabolic panel, fasting lipid profile, measurement of insulin and hemoglobin A_{1C} levels, assessments of thyroid and gonadal function, urinalysis, and a comprehensive physical performance assessment including measurement of body composition and neuromuscular system integrity.

Participation also involved a clinical evaluation consistent with the risk-based screening and surveillance recommended by the Children's Oncology Group (COG) guidelines.[8] The risk-based portion of the assessment included additional laboratory tests and evaluations of organ function (eg, echocardiography, pulmonary function testing, audiological testing, ophthalmologic evaluation, neurocognitive testing, bone mineral density testing).

Screening for Organ Dysfunction

Medical assessments were completed according to the COG guidelines, considering history of transfusion, exposure to specific chemotherapeutic agents or radiation affecting target organs and tissues, hematopoietic cell transplantation, and graft vs host disease. eTable 1 summarizes the number of survivors at risk for various outcomes based on exposure to specific therapeutic modalities, the screening test(s) for specific exposures, and criteria for positive screening by organ system. Precise criteria for positive screening outcomes are provided in eTable 2.

Screening for Subsequent Adult Neoplasms

Survivors treated with radiation were considered at risk for subsequent solid neoplasms. With the exception of colonoscopy in survivors treated with abdominal radiation, pelvic radiation, or both, and breast imaging in young women treated with chest radiation, risk-based screening for subsequent solid neoplasms involved history and physical examination. The complete blood cell count was used to assess for myelodysplasia and subsequent hematologic neoplasms in survivors treated with alkylating agents, anthracyclines, and epipodophyllotoxins.

Validation and Classification of Medical Events

Medical records were routinely obtained to validate selected medical conditions diagnosed before the SJLIFE evaluation, including all subsequent neoplasms, all major cardiovascular events, and other severe or chronic organ dysfunction. Medical records were also obtained after SJLIFE participation to confirm diagnoses of conditions identified or suspected from the preliminary results of screening evaluations. Chronic health conditions were classified using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 as mild (grade 1), moderate (grade 2), serious/disabling (grade 3), or life-threatening (grade 4).[9]

Statistical Analysis

Participants were compared with nonparticipants using *t* tests, χ^2 statistics, and Fisher exact tests. Percentages of participants with adverse organ system outcomes were calculated by exposure status and by whether the diagnosis occurred prior to, at, or after the SJLIFE visit for specific risk (exposure) categories, for any treatment-related risk, for no cancer treatment–related risk, and overall. Age- and sex-attributable fractions, reported as percentages with 95% confidence intervals, were calculated for adverse outcomes included in the core assessment battery.[10] These compare exposed survivors with nonexposed survivors within treatment categories, with treatment exposure preceding the health condition under consideration. A priori levels of significance were 2-tailed ($P < .05$). Kaplan-Meier methods were used to estimate the age-specific prevalence of adverse outcomes.[11] SAS version 9.2 (SAS Institute Inc) was used for all analyses.

RESULTS

Of 2843 patients confirmed eligible, 1837 (64.6%) enrolled in the study. This analysis included 1713 participants (60.3% of eligible) diagnosed and treated between 1962 and 2001, enrolled in the study since October 1, 2007, and undergoing follow-up until October 31, 2012, who had completed on-campus medical evaluations.

Nonparticipants included 680 who actively or passively elected not to participate, 277 who expressed interest in participating but had not completed their campus visit, 124 who completed questionnaires but did not receive on-campus medical assessment, and 49 lost to follow-up. TABLE 1 reports demographic characteristics of study participants and compares characteristics of survivors who completed a campus visit with nonparticipants presumed eligible. Survivors who did not complete campus evaluations were more likely to be men and older and to have a longer elapsed time from diagnosis and were somewhat less likely to have received radiation and selected treatment exposures than those who completed the clinical evaluation. eTable 3 summarizes selected chemotherapy and radiation-dose distributions of participants.

Risk-Based Medical Assessments

TABLE 2 and TABLE 3 summarize the prevalence of selected treatment-related toxic effects detected by risk-based screening associated with specific treatments. The overall prevalence of a given late effect represents the sum total of case participants with the condition diagnosed before the SJLIFE evaluation, directly as a result of the SJLIFE evaluation, and after but unrelated to the SJLIFE evaluation.

Prevalence and Severity of Organ Dysfunction

Impaired pulmonary, cardiac, endocrine, and nervous system function were most prevalent (detected in ≥20% of participants at risk). Among survivors exposed to pulmonary toxic cancer treatments, 65.2% (95% CI, 60.4%-69.8%) had abnormal pulmonary function, with 35.7% (95% CI, 31.1%-40.5%) identified during the SJLIFE evaluation. The highest prevalence occurred among those treated with lung radiation (74.4% [95% CI, 69.1%-79.2%]; eTable 1), followed by those treated with bleomycin (73.3% [95% CI, 61.9%-82.9%]) and thoracotomy (53.2% [95% CI, 44.1%-62.0%]).

Among survivors exposed to cardiotoxic therapies, 56.4% (95% CI, 53.5%-59.2%) had cardiac abnormalities, with such abnormalities newly discovered in 46.5% (95% CI, 43.6%-49.3%) as a result of the SJLIFE evaluation. Heart

Table 1. Demographic, Treatment Exposures, and Diagnostic Characteristics of SJLIFE Campus Visit Participants (n = 1713) and Nonparticipants (n = 1130)

Characteristic	No. (%) Total (N = 2843)	Participants (n = 1713)	Nonparticipants (n = 1130)	*P* Value[a]
Sex				
Women	1365 (48.0)	880 (51.4)	485 (42.9)	<.001
Men	1478 (52.0)	833 (48.6)	645 (57.1)	
Race				
White	2456 (86.4)	1493 (87.2)	963 (85.2)	.27
Black	360 (12.7)	203 (11.8)	157 (13.9)	
Other	27 (0.9)	17 (1.0)	10 (0.9)	
Hispanic ethnicity				
Yes	31 (1.1)	18 (1.1)	13 (1.1)	.80
No	2812 (98.9)	1695 (99.0)	1117 (98.9)	
Primary diagnosis[b]				
Leukemia				
Acute lymphoblastic	1204 (42.3)	765 (44.7)	439 (38.9)	
Acute myeloid	77 (2.7)	38 (2.2)	39 (3.5)	
Other	9 (0.3)	6 (0.4)	3 (0.3)	
Lymphoma				
Hodgkin	328 (11.5)	218 (12.7)	110 (9.7)	
Non-Hodgkin	155 (5.5)	78 (4.6)	77 (6.8)	
CNS tumors				
Astrocytoma or glioma	127 (4.5)	67 (3.9)	60 (5.3)	
Medulloblastoma and PNET	54 (1.9)	38 (2.2)	16 (1.4)	
Ependymoma	19 (0.7)	15 (0.9)	4 (0.4)	
Other	41 (1.4)	21 (1.2)	20 (1.8)	
Sarcoma				
Ewing sarcoma family of tumors	87 (3.1)	58 (3.4)	29 (2.6)	
Osteosarcoma	119 (4.2)	71 (4.1)	48 (4.3)	
Rhabdomyosarcoma	84 (3.0)	47 (2.7)	37 (3.3)	
Nonrhabdomyosarcoma	46 (1.6)	17 (1.0)	29 (2.6)	
Embryonal tumors				
Germ cell tumor	44 (1.5)	20 (1.2)	24 (2.1)	
Neuroblastoma	131 (4.6)	64 (3.7)	67 (5.9)	
Wilms tumor	160 (5.6)	94 (5.5)	66 (5.8)	
Other				
Hepatoblastoma	8 (0.3)	4 (0.2)	4 (0.4)	
Melanoma	5 (0.2)	4 (0.2)	1 (0.1)	
Retinoblastoma	109 (3.8)	66 (3.9)	43 (3.8)	
Carcinomas	27 (0.9)	16 (0.9)	11 (1.0)	
Other neoplasms	9 (0.3)	6 (0.4)	3 (0.3)	
Age at diagnosis, y				
Mean (SD)	7.5 (5.5)	7.5 (5.5)	7.4 (5.4)	
Median (range)	6.0 (0.0-28.0)	6.0 (0.0-24.0)	6.0 (0.0-28.0)	
<1	173 (6.1)	95 (5.6)	78 (6.9)	.49
1-4	958 (33.7)	591 (34.5)	367 (32.5)	
5-9	699 (24.6)	411 (24.0)	288 (25.5)	
10-14	597 (21.0)	359 (21.0)	238 (21.1)	
15-19	394 (13.9)	245 (14.3)	149 (13.2)	
20-24	22 (0.8)	12 (0.7)	10 (0.9)	
Time from diagnosis, y				
Mean (SD)	26.3 (7.8)	25.6 (7.6)	27.4 (7.9)	
Median (range)	25.8 (10.9-48.3)	25.1 (10.9-47.9)	27.2 (11.9-48.3)	
10-19	665 (23.4)	434 (25.3)	231 (20.4)	<.001
20-29	1276 (44.9)	789 (46.1)	487 (43.1)	
30-39	761 (26.8)	433 (25.3)	328 (29.0)	
40-49	141 (5.0)	57 (3.3)	84 (7.4)	

(continued)

Table 1. Demographic, Treatment Exposures, and Diagnostic Characteristics of SJLIFE Campus Visit Participants (n = 1713) and Nonparticipants (n = 1130) (continued)

Characteristic	No. (%) Total (N = 2843)	Participants (n = 1713)	Nonparticipants (n = 1130)	*P* Value[a]
Treatment exposure				
Radiation	1742 (61.3)	1108 (64.7)	634 (56.1)	<.001
Anthracyclines	1630 (57.3)	1001 (58.4)	629 (55.6)	.14
Alkylating agents	1723 (60.6)	1068 (62.4)	655 (57.9)	.02
Platinum	260 (9.1)	152 (8.9)	108 (9.6)	.54
Glucocorticoids	1513 (53.2)	964 (56.3)	549 (48.6)	<.001
Epipodophyllotoxins	1110 (39.0)	694 (40.5)	416 (36.8)	.05
Antimetabolites	1609 (56.6)	994 (58.0)	615 (54.4)	.06
Age at recruitment, y				
Mean (SD)	33.8 (8.2)	33.1 (8.1)	34.9 (8.4)	
Median (range)	33.3 (18.0-66.0)	32.0 (18.0-60.0)	34.0 (22.0-66.0)	
18-24	397 (14.0)	279 (16.3)	118 (10.4)	<.001
25-29	563 (19.8)	348 (20.3)	215 (19.0)	
30-34	657 (23.1)	390 (22.8)	267 (23.6)	
35-39	521 (18.3)	314 (18.3)	207 (18.3)	
40-44	380 (13.4)	221 (12.9)	159 (14.1)	
45-49	211 (7.4)	108 (6.3)	103 (9.1)	
50-66	114 (4.0)	53 (3.1)	61 (5.4)	
Duration of follow-up, y				
Before SJLIFE visit				
Mean (SD)		25.6 (7.6)		
Median (IQR)		25.1 (19.9-31.2)		
After SJLIFE visit				
Mean (SD)		2.8 (0.9)		
Median (IQR)		2.8 (2.1-3.5)		

Abbreviations: CNS, central nervous system; IQR, interquartile range; PNET, primitive neuroectodermal tumor; SJLIFE, St Jude Lifetime Cohort Study.

[a] From χ^2 test comparing participants with nonparticipants.

[b] The distribution of cancer diagnoses among cancer survivors diagnosed before age 20 years in the United States is estimated to be 18.3% for leukemia, 18.7% for lymphoma, 14.6% for CNS tumors, 11.8% for sarcoma, 16.6% for embryonal tumors, and 8.2% for other diagnoses (Surveillance, Epidemiology, and End Results [SEER] Program [http://www.seer.cancer.gov] research data 1973-2009, National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch, released April 2012, based on the November 2011 submission).

valve abnormalities, most frequently mild to moderate tricuspid regurgitation, mitral valve regurgitation, or both, were diagnosed in 56.7% (95% CI, 52.2%-61.1%) of survivors exposed to cardiac-directed radiation. The prevalence of systolic dysfunction among survivors exposed to anthracyclines, cardiac-directed radiation therapy, or both was 6.2% (95% CI, 5.0%-7.8%).

Sixty-two percent (95% CI, 59.5%-64.5%) of survivors developed endocrine disorders. Hypothalamic-pituitary axis (HPA) or thyroid dysfunction was diagnosed before SJLIFE participation in more than 90%. The prevalence was 56.4% (95% CI, 52.5%-60.1%) for disorders affecting the HPA, 13.8% (95% CI, 11.6%-16.1%) for disorders affecting the thyroid, 66.4% (95% CI, 61.1%-71.6%) for disorders affecting male gonadal function, and 11.8% (95% CI, 9.2%-14.7%) for disorders affecting female gonadal function for participants exposed to radiation affecting these organs, to alkylating agents, or to both.

Nervous system abnormalities included a spectrum of neurosensory, neurocognitive, and neurological deficits. The most common adverse neurosensory outcome was hearing loss, prevalent among 62.1% (95% CI, 55.8%-68.2%) of survivors exposed to platinum agents or ear irradiation. Cataracts were detected in 20.6% (95% CI, 18.3%-23.1%) of the population exposed to eye radiation, glucocorticoids, or busulfan; 28.5% (95% CI, 23.1%-33.9%) of persons with cataracts and glucocorticoid exposure had not received eye irradiation.

The prevalence of any neurocognitive impairment among survivors exposed to central nervous system treatment was 48.0% (95% CI, 44.9%-51.0%). The most frequent deficits were in mathematics (29.2% [95% CI, 25.6%-32.8%]), memory (25.4% [95% CI, 21.9%-28.9%]), and processing speed (24.4% [95% CI, 21.0%-27.8%]). Peripheral neuropathy was identified in 21.9% (95% CI, 19.8%-24.2%) of survivors treated with vinca alkaloid or platinum chemotherapy.

In contrast, the prevalence of hematopoietic, hepatic, skeletal, and urinary tract dysfunction was less than 20% (Table 3 and eTable 1). The prevalence of a positive liver dysfunction screen result was 13.0% (95% CI, 10.8%-15.3%) among at-risk survivors treated with antimetabolite chemotherapy or liver irradiation. Hepatitis C was the most common transfusion-acquired infection, affecting 6.8% (95% CI, 5.5%-8.2%) of those at risk. Risk-based screening identified 1.0% (95% CI, 0.5%-1.6%) of hepatitis C cases not previously diagnosed. Assessment of skeletal toxicity was limited to bone mineral density testing; osteoporosis was identified in only 9.6% (95% CI, 8.0%-11.5%) of those treated with glucocorticoids, methotrexate, or radiation to the HPA. The overall prevalence of kidney dysfunction was 5.0% (95% CI, 4.0%-6.3%), divided equally between those with a previously established diagnosis of chronic kidney disease and those presenting with occult kidney dysfunction identified by the SJLIFE laboratory evaluation. Abnormalities of blood cell counts were detected in only 3.0% (95% CI, 2.1%-3.9%) of survivors at risk for secondary leukemia following treatment with alkylating agents, anthracycline, or epipodophyllotoxin chemotherapy.

In this clinically evaluated cohort, 98.2% (95% CI, 97.5%-98.8%) of participants had a chronic health condition. Distributions of chronic health conditions by CTCAE version 4 grades are reported in eTable 4. A serious/disabling or life-threatening chronic health condition (grade 3-4) occurred in 67.6% (95% CI, 65.3%-69.8%) of survivors. The overall cumulative preva-

lence of a chronic condition was estimated to be 95.5% (95% CI, 94.8%-98.6%) by age 45 years and 93.5% (95% CI, 86.7%-97.3%) 35 years after cancer diagnosis. The cumulative prevalence of a grade 3-4 chronic condition was estimated to be 80.5% (95% CI, 73.0%-86.6%) at age 45 years and 75.1% (95% CI, 68.0%-80.9%) at 35 years after cancer.

Percentage of Adverse Outcomes Associated With Treatment Exposure

For conditions detected by comprehensive screening with the core battery of evaluations, TABLE 4 summa-

Table 2. Prevalence of Cardiovascular, Pulmonary, and Endocrine or Reproductive Late Effects in At-Risk Populations Following Exposure-Based Screening

Potential Late Effect	Screening Test	Exposure Status	No. at Risk[a]	No. (%) [95% CI]				CTCAE Version 4 Grade 3-4, %[b]
				SJLIFE Diagnosis			Overall Prevalence	
				Before	Related	After		
Cardiovascular								
Cardiomyopathy	Echocardiogram	Anthracyclines, anthraquinones, radiation to heart	1214	32 (2.6) [1.8-3.7]	38 (3.1) [2.2-4.3]	6 (0.5) [0.2-1.1]	76 (6.2) [5.0-7.8]	60.5
Heart valve disorder	Echocardiogram	Radiation to heart	501	31 (6.2) [4.2-8.7]	235 (46.9) [42.5-51.4]	18 (3.6) [2.1-5.6]	284 (56.7) [52.2-61.1]	9.9
Conduction disorder	Electrocardiogram	Anthracyclines, anthraquinones, radiation to heart	1214	13 (1.1) [0.6-1.8]	154 (12.7) [10.9-14.7]	2 (0.2) [0.0-0.6]	169 (14.0) [12.0-16.0]	2.4
Any cardiac condition	As indicated above	Any cancer treatment–related risk	1214	64 (5.3) [4.1-6.7]	564 (46.5) [43.6-49.3]	56 (4.6) [3.5-5.9]	684 (56.4) [53.5-59.2]	NA
Cardiovascular risk factors								
Hypertension	Blood pressure	Ifosfamide, cisplatin/carboplatin, methotrexate, radiation to kidney, nephrectomy, radiation to HPA	1508	232 (15.4) [13.6-17.3]	94 (6.2) [5.1-7.6]	16 (1.1) [0.6-1.7]	342 (22.7) [20.6-24.9]	0.6
Dyslipidemia	Fasting lipid panel	Cisplatin/carboplatin, radiation to HPA	807	186 (23.0) [20.2-26.1]	256 (31.7) [28.5-35.1]	49 (6.1) [4.5-7.9]	491 (60.8) [57.4-64.2]	0
Obesity	Body mass index	Radiation to HPA	714	158 (22.1) [19.1-25.4]	187 (26.2) [23.0-29.6]	0	345 (48.3) [44.6-52.1]	100
Pulmonary								
Abnormal pulmonary function	Pulmonary function tests	Busulfan, carmustine/lomustine, bleomycin, radiation to lungs, thoracotomy	417	121 (29.0) [24.7-33.6]	149 (35.7) [31.1-40.5]	2 (0.5) [0.1-1.7]	272 (65.2) [60.4-69.8]	21.0
Endocrine or reproductive								
HPA disorders (≥1)	Screening for HPA deficiencies: growth and pubertal progress, menstrual history, IGF-1, 8-AM serum cortisol, LH, FSH, estradiol or morning testosterone, TSH, free T_4	Radiation to HPA (dose ≥18 Gy)	685	171 (25.0) [21.7-28.2]	211 (30.8) [27.3-34.3]	4 (0.6) [0.4-1.1]	386 (56.4) [52.6-60.1]	NA
Diabetes mellitus	Fasting serum glucose	Radiation to HPA	714	35 (4.9) [3.4-6.8]	13 (1.8) [1.0-3.1]	8 (1.1) [0.5-2.2]	56 (7.8) [6.0-10.1]	32.0
Primary hypothyroidism[c]	TSH	Radiation to neck	910	117 (12.9) [10.8-15.2]	7 (0.8) [0.3-1.6]	1 (0.1) [0.0-0.6]	125 (13.8) [11.6-16.1]	0
Primary ovarian failure[d]	Menstrual history, FSH, estradiol	Alkylating agents, radiation to female reproductive system	553	44 (8.0) [5.8-10.5]	20 (3.6) [2.2-5.5]	1 (0.2) [0.0-1.0]	65 (11.8) [9.2-14.7]	0
Male germ cell dysfunction[e]	Semen sample analysis	Alkylating agents, radiation to male reproductive system	328	9 (2.7) [1.3-5.1]	209 (63.7) [58.3-68.9]	0	218 (66.4) [61.1-71.6]	97.7
Leydig cell failure[f]	Morning testosterone, LH	Alkylating agents, radiation to male reproductive system	574	25 (4.4) [2.8-6.4]	37 (6.4) [4.6-8.8]	4 (0.7) [0.2-1.8]	66 (11.5) [9.0-14.4]	0
Any endocrine condition	As indicated above	As indicated above	1423	531 (37.3) [34.8-39.9]	332 (23.3) [21.2-25.6]	20 (1.4) [0.9-2.2]	883 (62.0) [59.5-64.6]	NA

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; FSH, follicle-stimulating hormone; HPA, hypothalamic-pituitary axis; IGF-1, insulin growth factor 1; LH, lutenizing hormone; NA, not applicable; SJLIFE, St Jude Lifetime Cohort Study; TSH, thyroid-stimulating hormone; T_4, thyroxine.

[a] At risk by treatment exposure as defined in the Children's Oncology Group (COG) guidelines; see eTable 1 at http://www.jama.com for detailed exposures and potential late effects evaluated by risk-based screening.

[b] Percentages include only those participants who fulfill criteria for "at risk" as defined by the COG guidelines.

[c] Excluding 39 patients with prior thyroidectomy.

[d] Excluding 50 women with bilateral oophorectomy.

[e] Excluding 246 at-risk patients who declined semen analysis because of history of established fertility (81), infertility (43), inability to provide a sample (18), or personal reasons (107).

[f] Excluding 1 man with bilateral orchiectomy.

rizes the prevalence of chronic health conditions by exposure to specific high-risk treatment as defined by the COG guidelines, and the fraction attributable to the exposure. Cancer treatment was associated with a high proportion (88.4%-100%) of cases of endocrinopathy, although the attributable fraction associated with diabetes mellitus was lower (41.7% [95% CI, 12.2%-61.3%]). Risk factors for cardiovascular disease (eg, hypertension, dyslipidemia, obesity) were highly prevalent among both exposed and unexposed survivor groups and, as such, had a smaller proportion of cases associated with cancer treatment. Other conditions with a high percentage of cases associated with cancer treatment included kidney dysfunction (attributable fraction, 65.7% [95% CI, 21.7%-85.0%]) and cardiac ischemia (attributable fraction, 57.1% [95% CI, 36.4%-71.0%]). In contrast, the preva-

Table 3. Prevalence of Neurocognitive, Neurosensory, Metabolic, and Transfusion-Associated Infectious Late Effects in At-Risk Populations Following Exposure-Based Screening

				No. (%) [95% CI]				
				SJLIFE Diagnosis				
Potential Late Effect	Screening Test	Exposure Status	No. at Risk[a]	Before	Related	After Prevalence	Overall	CTCAE Version 4 Grade 3-4, %[b]
Neurocognitive								
Neurocognitive impairment	Neuropsychological testing	Antimetabolite therapy, cranial irradiation, neurosurgery	1062	90 (8.5) [6.9-10.3]	415 (39.1) [36.1-42.1]	4 (0.4) [0.1-1.0]	509 (48.0) [44.9-51.0]	58.4
Neurosensory								
Ocular toxicity	Ophthalmology consultation	Busulfan, corticosteroids, radiation to eye	1127	120 (10.6) [8.9-12.6]	183 (16.2) [14.1-18.5]	9 (0.8) [0.4-1.5]	312 (27.6) [25.1-30.4]	17.0
Hearing loss	Otoscopy, tympanometry, and conventional pure-tone audiometry	Cisplatin/carboplatin, radiation to ear (dose >30 Gy)	251	116 (46.2) [39.9-52.6]	38 (15.1) [10.9-20.2]	2 (0.8) [0.1-2.8]	156 (62.1) [55.8-68.2]	53.8
Neuropathy	Modified Total Neuropathy Scale	Cisplatin/carboplatin, vinblastine/ vincristine	1422	55 (3.9) [2.9-5.0]	241 (16.9) [15.0-19.0]	16 (1.1) [0.6-1.8]	312 (21.9) [19.8-24.2]	1.9
Metabolic								
Abnormal blood cell counts	Complete blood cell count with differential	Alkylating agents, anthracyclines, epipodophyllotoxins	1375	16 (1.2) [0.7-1.9]	20 (1.5) [0.9-2.2]	4 (0.3) [0.1-0.7]	40 (3.0) [2.1-3.9]	0
Liver dysfunction	ALT, AST, bilirubin	Mercaptopurine/ thioguanine, radiation to liver (dose ≥30 Gy)	920	34 (3.7) [2.6-5.1]	65 (7.1) [5.5-8.9]	20 (2.2) [1.3-3.3]	119 (13.0) [10.8-15.3]	20.0
Osteoporosis	Dual-energy x-ray absorptiometry	Methotrexate, corticosteroids, radiation to HPA	1142	23 (2.0) [1.3-3.0]	87 (7.6) [6.1-9.3]	0	110 (9.6) [8.0-11.5]	100
Kidney dysfunction	Urinalysis, BUN, creatinine, sodium, potassium, chloride, CO_2, calcium, magnesium, phosphate	Ifosfamide, cisplatin/ carboplatin, methotrexate, radiation to kidney, nephrectomy	1410	35 (2.5) [1.7-3.4]	33 (2.3) [1.6-3.3]	3 (0.2) [0.0-0.6]	71 (5.0) [4.0-6.3]	15.2
Infection, transfusion acquired								
Hepatitis B	Hepatitis B surface antigen and core antibody	Diagnosis before 1972	113	2 (1.8) [0.2-6.2]	1 (0.9) [0.0-4.8]	1 (0.9) [0.0-4.8]	4 (3.6) [1.0-8.8]	0.25
Hepatitis C	Hepatitis C antibody	Diagnosis before 1993	1437	75 (5.2) [4.1-6.5]	14 (1.0) [0.5-1.6]	8 (0.6) [0.2-1.1]	97 (6.8) [5.5-8.2]	43.3
HIV	HIV serology (HIV 1 and 2 antibodies)	Diagnosis between 1977-1985	640	2 (0.3) [0.0-1.1]	1 (0.2) [0.0-0.9]	0	3 (0.5) [0.1-1.4]	100
Cancer screening								
Subsequent neoplasm[c]	Targeted screening based on risk of specific subsequent neoplasm[d]	Any cancer treatment–related risk	1536	202 (13.2) [11.5-14.9]	43 (2.8) [2.0-3.8]	30 (2.0) [1.3-2.8]	275 (18.0) [16.0-19.9]	NA

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CO_2, carbon dioxide; CTCAE, Common Terminology Criteria for Adverse Events; HIV, human immunodeficiency virus; HPA, hypothalamus-pituitary axis; NA, not applicable; SJLIFE, St Jude Lifetime Cohort Study.

[a] At risk by treatment exposure as defined in the Children's Oncology Group (COG) guidelines; see eTable 1 at http://www.jama.com for detailed exposures and potential late effects evaluated by risk-based screening.

[b] Percentages include only those participants who fulfill criteria for "at risk" as defined by COG guidelines.

[c] The total prevalence percentages for subsequent neoplasm count each person only once. Two participants had a second neoplasm diagnosed both before and at SJLIFE visit and another participant had a second neoplasm diagnosed before and after SJLIFE visit.

[d] Complete blood cell count for myelodysplasia or acute myeloid leukemia, mammography or breast magnetic resonance imaging for breast cancer, colonoscopy for colorectal cancer, physical examination for other skin or solid neoplasms.

Table 4. Chronic Health Conditions and Percentage Associated With Cancer-Related Therapy[a]

Potential Late Effect	Screening Test	Criteria for Positive Screening[b]	Exposure Groups	No./Total	% (95% CI)	
					Prevalence	Attributable Fraction[c]
Cardiovascular risk factors						
Hypertension	Blood pressure	Blood pressure >140/90 mm Hg	Total	387/1713	22.6 (20.6 to 24.7)	9.3 (−16.3 to 29.2)
			Exposed	342/1508	22.7 (20.6 to 24.9)	
			Unexposed	45/205	22.0 (16.5 to 28.3)	
Dyslipidemia	Fasting lipid panel	Total cholesterol ≥200 mg/dL, triglycerides ≥150 mg/dL, LDL-C ≥130 mg/dL, or HDL-C <40 mg/dL	Total	872/1713	50.9 (48.5 to 53.3)	15.5 (10.2 to 20.5)
			Exposed	491/807	60.8 (57.4 to 64.2)	
			Unexposed	381/906	42.1 (38.8 to 45.3)	
Obesity	BMI	BMI >30.0[d]	Total	624/1713	36.5 (34.1 to 38.8)	42.1 (34.4 to 48.9)
			Exposed	345/714	48.3 (44.6 to 52.1)	
			Unexposed	279/999	27.9 (25.2 to 30.8)	
Cardiac						
Arrhythmia	Electrocardiogram	Detection of rhythm abnormality	Total	126/1713	7.4 (6.2 to 8.7)	−17.8 (−68.4 to 17.7)
			Exposed	85/1214	7.0 (5.6 to 8.6)	
			Unexposed	41/499	8.2 (6.0 to 11.0)	
Conduction disorder	Electrocardiogram	Detection of conduction abnormality	Total	243/1713	14.2 (12.6 to 15.9)	−4.3 (−33.9 to 18.8)
			Exposed	169/1214	14.0 (12.0 to 16.0)	
			Unexposed	74/499	14.8 (11.8 to 18.3)	
History of cardiac ischemia	Electrocardiogram	Electrocardiographic abnormality indicating history of ischemia	Total	387/1713	5.7 (20.6 to 24.7)	57.1 (36.4 to 71.0)
			Exposed	48/501	9.6 (7.2 to 12.5)	
			Unexposed	49/1212	4.1 (3.0 to 5.3)	
Endocrine or reproductive						
Hypogonadotropic hypogonadism (women)[e]	Menstrual history, FSH, estradiol	Amenorrhea before 40 y, estradiol below normal range, and FSH within or below normal range	Total	34/830	4.1 (2.9 to 5.7)	90.7 (83.2 to 94.9)
			Exposed	20/65	30.8 (19.9 to 43.5)	
			Unexposed	14/765	1.8 (1.0 to 3.1)	
Hypogonadotropic hypogonadism (men)	LH, morning testosterone	Testosterone below normal range and LH within or below normal range	Total	55/832	6.5 (5.1 to 8.5)	88.4 (80.1 to 93.3)
			Exposed	23/88	26.2 (17.3 to 36.6)	
			Unexposed	32/744	4.3 (3.0 to 6.0)	
Central hypothyroidism[f]	TSH, free T_4	Free T_4 below normal range and TSH within or below normal range	Total	78/1674	4.7 (3.7 to 5.8)	96.6 (89.2 to 98.9)
			Exposed	38/152	25.0 (18.3 to 32.7)	
			Unexposed	40/1522	2.7 (1.9 to 3.6)	
Diabetes mellitus	Fasting serum glucose, hemoglobin A_{1C}	Fasting glucose ≥126 mg/dL or hemoglobin A_{1C} ≥6.4%	Total	101/1713	5.9 (4.8 to 7.1)	41.7 (12.2 to 61.3)
			Exposed	56/714	7.8 (6.0 to 10.1)	
			Unexposed	45/999	4.5 (3.3 to 6.0)	
Primary hypothyroidism[f]	TSH, free T_4	Free T_4 below normal range and TSH above normal range	Total	128/1674	7.7 (6.4 to 9.0)	97.0 (90.6 to 99.0)
			Exposed	125/910	13.8 (11.6 to 16.2)	
			Unexposed	3/764	0.4 (0.1 to 1.1)	
Primary ovarian failure[e]	Menstrual history, FSH, estradiol	Amenorrhea before age <40 y and FSH above normal range	Total	65/830	7.8 (6.1 to 9.9)	100.0
			Exposed	65/553	11.8 (9.2 to 14.7)	
			Unexposed	0/277	0	
Leydig cell failure[g]	Morning testosterone, LH	Testosterone below normal range and LH above normal range	Total	71/832	8.5 (6.7 to 10.6)	96.5 (91.2 to 98.6)
			Exposed	66/574	11.5 (9.0 to 14.4)	
			Unexposed	5/258	2.0 (0.6 to 4.5)	
Hematologic						
Abnormal blood cell counts	Complete blood cell count with differential	Abnormal blood cell counts consistent with cytopenia, myelodysplasia, myeloproliferative disorder	Total	49/1713	2.9 (2.1 to 3.8)	5.6 (−96.8 to 54.8)
			Exposed	40/1375	3.0 (2.1 to 3.9)	
			Unexposed	9/338	2.7 (1.2 to 5.0)	
Hepatic						
Liver dysfunction	ALT, AST, bilirubin	ALT, AST, bilirubin above reference range	Total	205/1713	12.0 (10.5 to 13.6)	14.5 (−10.7 to 33.9)
			Exposed	119/920	13.0 (10.8 to 15.3)	
			Unexposed	86/793	10.9 (8.8 to 13.2)	
Neurosensory						
Neuropathy	Modified Total Neuropathy Scale	Score ≥4 on Modified Total Neuropathy Scale	Total	348/1713	20.4 (18.4 to 22.3)	42.3 (20.6 to 58.1)
			Exposed	312/1422	21.9 (19.8 to 34.2)	
			Unexposed	36/291	12.4 (8.8 to 16.7)	

(continued)

Table 4. Chronic Health Conditions and Percentage Associated With Cancer-Related Therapy[a] (continued)

Potential Late Effect	Screening Test	Criteria for Positive Screening[b]	Exposure Groups	No./Total	% (95% CI) Prevalence	% (95% CI) Attributable Fraction[c]
Urinary tract						
Kidney dysfunction	Urinalysis, BUN, creatinine, sodium, potassium, chloride, CO_2, calcium, magnesium, phosphate	Serum creatinine >1.5 mg/dL, eGFR <90 mL/min per 1.73m^2 with or without abnormal urinalysis (eg, proteinuria) with or without electrolyte alterations	Total	76/1713	4.5 (3.5 to 5.5)	65.7 (21.7 to 85.0)
			Exposed	71/1410	5.0 (4.0 to 6.3)	
			Unexposed	5/303	1.6 (0.5 to 3.8)	
Hemorrhagic cystitis (microscopic hematuria)	Urinalysis	Hematuria	Total	15/1713	0.9 (0.5 to 1.4)	−128.6 (−534.0 to 17.6)
			Exposed	7/1130	0.7 (0.3 to 1.3)	
			Unexposed	8/583	1.4 (0.6 to 2.7)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CO_2, carbon dioxide; eGFR, estimated glomerular filtration rate; FSH, follicle-stimulating hormone; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; T_4, thyroxine.

SI conversion factors: To convert total cholesterol, LDL-C, and HDL-C to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; creatinine to μmol/L, multiply by 88.4; and glucose to mmol/L, multiply by 0.0555.

[a] Table summarizes prevalence of chronic health conditions detected by comprehensive screening with the core battery of evaluations administered to all study participants.

[b] See eTable 3 at http://www.jama.com for detailed information about the definitions for positive screening for specific late effects.

[c] Attributable fraction (A_e%) indicates the percentage of cases in the cohort that are related to the specific treatment exposure, calculated as $Ae\% = (R_e - R_o)/R_e \times 100$, where R_e indicates absolute risk in exposed persons and R_o indicates absolute risk in unexposed persons. Negative values indicate that the risk for that chronic condition was less in the group that received the treatment exposure than in the group that did not receive the treatment exposure.

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] Results presented for evaluation of hypogonadotropic hypogonadism and primary ovarian failure exclude 50 women with bilateral oophorectomy.

[f] Results presented for evaluation of central and primary hypothyroidism exclude 39 patients with prior thyroidectomy.

[g] Results presented for evaluation of Leydig cell failure exclude 1 man with bilateral orchiectomy.

lence of arrhythmia or conduction disorders was not associated with cardiotoxic treatment exposures in survivors.

Cumulative Prevalence of Chronic Health Conditions

The FIGURE and eFigure 2 show the age-specific and time-from-cancer prevalence of chronic health conditions for certain organ-specific outcomes. The estimated prevalence of specific conditions was substantially higher following risk-based screening, highlighting the subclinical nature of many outcomes. For example, the estimated prevalence of a heart valve disorder among those aged 40 years treated with chest radiation increased from 5.7% (95% CI, 3.5%-7.9%) to 37.2% (95% CI, 33.0%-41.4%) after echocardiographic screening. In contrast, risk-based screening had little influence on the estimated prevalence for pituitary disorders; diagnoses of most of these conditions were established before SJLIFE participation.

Prevalence of Subsequent Neoplasms

A total of 272 survivors developed 1 or more subsequent neoplasms, including 335 solid and 13 hematologic neoplasms (eTable 5). For subsequent neoplasms identified directly as a result of the SJLIFE evaluation, abnormalities on physical examination (n=17), laboratory testing (n=2), and imaging (n=13) facilitated detection of 32 of 44 cases. Suspicious skin lesions were the most common physical finding leading to diagnosis of subsequent neoplasm, followed by palpable masses and abnormal mental status. Detection of hematuria on urinalysis among survivors treated with nephrotoxic chemotherapy led to diagnosis of 2 cases of renal cell carcinoma. Follow-up of imaging abnormalities led to diagnosis of breast cancer in 13 women; none of the lesions was palpable on examination. In addition, 12 survivors had subsequent neoplasms identified as incidental findings on risk-based screening (eg, renal cell mass detected on bone density testing) or imaging performed in the context of other research studies (eg, meningiomas detected on magnetic resonance imaging of the brain).

DISCUSSION

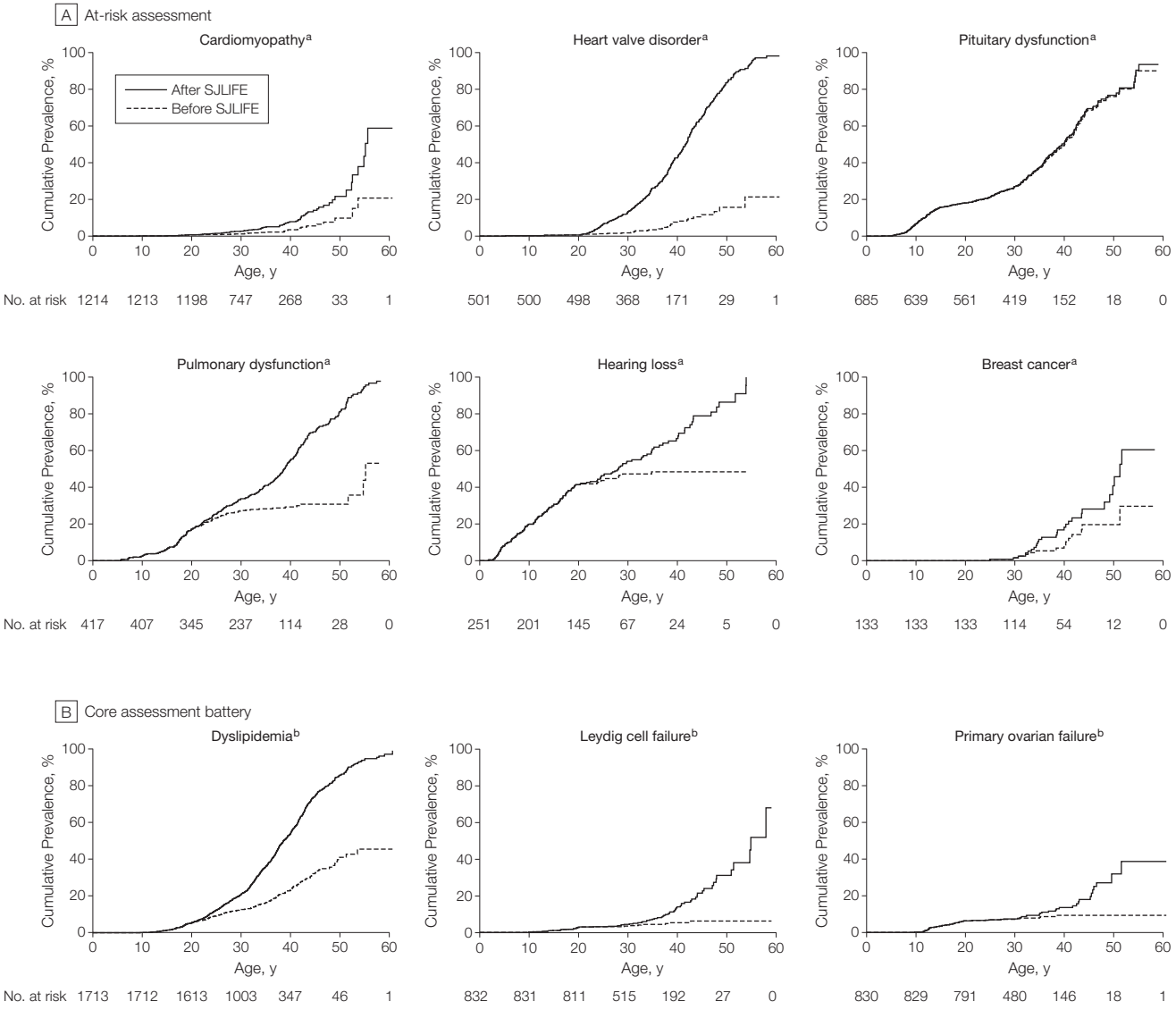
This report delineates the type and prevalence of specific health conditions systematically ascertained across multiple organ systems among a large, histologically heterogeneous population of adults formerly treated for childhood cancer. In contrast to published studies, SJLIFE prospectively applied consistent risk-based screening to quantify the burden of chronic disease among long-term survivors of childhood cancer. These results provide precise estimates of the prevalence of treatment-related morbidities among long-term survivors of childhood cancer and an enumeration of the chronic health conditions known to be associated with early mortality in the general population. In contrast to previous publications, the present study also quantifies the substantial proportion of previously undiagnosed disease among cohort members, underscoring the need for ongoing follow-up and assessment.

Prior studies investigating long-term outcomes of adults treated for cancer during childhood have largely relied on survivor self-report of outcomes or registry data.[2-5] Research programs in the United States reporting outcomes based on medical assessments have featured relatively small cohorts, including those with pediatric-aged survivors.[12-14] A previous study retrospectively evaluated the prevalence of adverse outcomes identified through clinic evaluations of late effects undertaken from

1996 to 2004 among 1362 five-year survivors of childhood cancer (median age, 24.4 years) in the Netherlands.[1] Medical assessments were performed according to standardized follow-up protocols; however, specific screening methods and total numbers screened for each condition were not described. The findings confirmed the burden of morbidity present in a young adult cohort (88% were younger than 35 years). At a mean follow-up of 17 years, 75% of survivors experienced at least 1 adverse event; 40% had at least 1 severe/disabling or life-threatening event.

Our results extend these findings in an older survivor population by documenting yield from risk-based screening according to standardized guidelines and by demonstrating the age-specific burden of particular chronic health conditions followed up for a mean of 26.3 years from diagnosis. Moreover, the focus on exposure-driven, risk-based screening increases the relevance of our findings, considering that despite the substantial evo-

Figure. Cumulative Prevalence of Chronic Health Conditions for Representative Groups of Organ-Specific Outcomes According to Age



Curves reflect cumulative prevalences based on proportion of participants diagnosed with a condition before and after participation in the St Jude Lifetime Cohort Study (SJLIFE) and undergoing follow-up until October 31, 2012.

[a] For cardiomyopathy, *at risk* defined as radiation therapy to the heart or exposure to anthracycline or anthroquinone; for heart valve disorder, as radiation to the heart; for pituitary dysfunction, as radiation (≥18 Gy) to the hypothalamus-pituitary; for pulmonary dysfunction, as thoracotomy, radiation to the lungs, or exposure to bisulfan, carmustine/lomustine, or bleomycin; for hearing loss, as radiation (≥30 Gy) to the ear or exposure to cisplatin or carboplatin; for breast cancer, as female sex and radiation (≥20 Gy) to the breast.

[b] As part of the core assessment battery, all participants were evaluated for dyslipidemia and gonadal failure.

lution of therapeutic approach for various pediatric malignancies over the last 50 years, most of the specific treatment modalities prompting screening remain in use.[15,16] Analyses evaluating outcomes related to the evolution of packaging these modalities over time and its influence on the prevalence of organ-specific outcomes for clinical diagnostic groups will be the subject of future investigations.

For some organ systems evaluated, the results of risk-based assessment revealed a substantial number of previously undiagnosed problems typically observed in older populations.[17-21] This had a marked effect on the estimates of age-specific organ dysfunction. Comparing the prevalences of our outcomes with those reported in previously published studies is difficult because the latter often represent clinically manifest conditions,[2-5] those derived from inconsistent screening practices administered over a long period,[1] or those applied to convenience cohorts.[13,14] Recent studies implementing systematic screening in younger survivor cohorts have similarly identified a high prevalence of abnormalities after selected systems (eg, pulmonary) were evaluated.[13] In our cohort, the prevalence of newly discovered neurocognitive and neurosensory deficits, heart valve disorders, and pulmonary dysfunction were particularly striking. Considering that the median age of this cohort was only 32 years, these data are concerning and may indicate a pattern of accelerated or premature aging. Evaluation of the contribution of predisposing host and treatment factors to this phenomenon will be the focus of future research in th SJLIFE cohort.

The primary aim of our study was to establish the prevalence of late health effects following systematic screening after predisposing cancer treatment–related exposures, with a particular emphasis on preclinical disease manifestations. For analytical purposes, we dichotomized screening outcomes, which included a spectrum of conditions of varying severity, as present or absent. Ninety-eight percent of our cohort had 1 or more chronic health conditions, with 67.6% having a severe/disabling or life-threatening condition by CTCAE version 4.0 (grade 3-4). Although some findings may not immediately influence the health status of survivors, their presence may reflect early disease outcomes that may be remediated or at least monitored prospectively to assess the relationship to future decline in function. For example, adult survivors of childhood leukemia who received 24-Gy cranial irradiation demonstrated reduced cognitive status and memory on formal neuropsychological testing.[22] The abnormalities detected did not affect functional status measures such as employment but are consistent with early-onset mild cognitive dementia, underscoring the need for longitudinal evaluation as this group ages.

Exposure-specific, risk-based screening resulted in identification and referral for treatment of some conditions that are amenable to remediation. These included low-stage occult breast cancers identified by breast imaging in women treated with chest radiation and cardiomyopathy identified by echocardiography among those exposed to anthracyclines and chest radiation. In contrast, the yield from screening for other outcomes (eg, myelodysplasia and kidney dysfunction) was negligible. Low yield from laboratory assessments of hematologic and biochemical parameters has been reported in a younger survivor cohort undergoing follow-up for slightly more than 10 years.[13] Confirmation of these findings in this older and larger cohort provides reassurance that these conditions do not increase in prevalence with aging. Collectively, the data from risk-based screening also provide clinically relevant information about the magnitude of risk and preclinical manifestations of common late effects to guide refinement of health screening recommendations.

Assessment of all survivors with a core laboratory battery permitted evaluation of associations of specific cancer treatment and chronic health conditions. As expected, endocrine and reproductive disorders were largely associated with previous treatment with radiation and alkylating agents. The association of cancer treatment with conditions highly prevalent in the general population, such as obesity and diabetes, was lower. For example, an increased risk of the metabolic syndrome or its components has been observed among cancer survivors treated with HPA irradiation.[23] However, within the SJLIFE cohort, the attributable fraction of obesity, diabetes mellitus, dyslipidemia, and hypertension ranged from 9% to 42% among survivors. The current report describes the occurrence of health outcomes within survivors of childhood cancer following the initial cross-sectional clinical assessment. In-depth analyses are under way to identify predictors of and risk profiles for specific outcomes, which take into consideration the interrelationships between genetics, demographic and lifestyle factors, treatment exposures, and comorbidities. The ongoing prospective follow-up of these patients will also provide additional insights into longitudinal changes in health outcomes within an aging survivor population.

These findings should be considered in the context of study limitations. Results could be influenced by selection bias, considering the 60% participation rate for on-site comprehensive evaluations. However, the lack of substantial differences between the studied and the source population of SJLIFE in the relative frequencies of demographic, disease, or neighborhood characteristics reduces concerns about selective nonparticipation.[7] It is possible that differences in attained age and time from diagnosis between participants and nonparticipants could bias results if the older nonparticipants who had a greater elapsed time from treatment had more chronic health conditions.

Because of enrollment priorities based on treatment exposures in this dynamic cohort, the study population does not precisely reflect the distribution of histological characteristics that would be expected in a cohort of long-term survivors of childhood cancer. For example, the proportion of those with leu-

kemia is somewhat higher, and the proportion of those with brain cancer is lower than would be anticipated in a large random sample of survivors. Those relative proportions will tend to balance as recruitment and enrollment in this ongoing study continue over time.

In addition, the yield of screening is likely underestimated in the SJLIFE cohort because many participants had been previously screened as participants in the pediatric long-term follow-up clinic at St Jude. Moreover, the absence of controls in our study precluded assessment of the actual clinical effect of screening. Failure to undertake uniform evaluations among all cohort participants also precluded the discovery of novel treatment-related outcomes.

Last, when interpreting the cumulative prevalence within our population, it is important to keep in mind that the rates are based on the experience of patients alive at the time of recruitment for clinical evaluation. Thus, these prevalence rates underestimate actual incidence if one assumes that the population of patients who met eligibility criteria but who died prior to recruitment to the SJLIFE cohort experienced a high rate of morbidity prior to death. This assumption seems reasonable because reports of late mortality among survivors of childhood cancer have indicated that second cancers, cardiac events, and pulmonary events are the most frequent causes of death.[24]

In summary, this study provides global and age-specific estimates of clinically ascertained morbidity in multiple organ systems in a large systematically evaluated cohort of long-term survivors of childhood cancer. The percentage of survivors with 1 or more chronic health conditions prevalent in a young adult population was extraordinarily high. These data underscore the need for clinically focused monitoring, both for conditions that have significant morbidity if not detected and treated early, such as second malignancies and heart disease, and also for those that if remediated can improve quality of life, such as hearing loss and vision deficits.

Author Contributions: Drs Hudson and Ness had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Hudson and Ness contributed equally to the manuscript.
Study concept and design: Hudson, Gurney, Krull, Armstrong, Srivastava, Robison.
Acquisition of data: Hudson, Ness, Gurney, Chemaitilly, Krull, Armstrong, Nottage, Robison.
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Drafting of the manuscript: Hudson, Ness, Mulrooney, Chemaitilly, Green, Armstrong, Nottage, Srivastava, Robison.
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